Rotavirus Genotypes and Severity of Diarrheal Disease

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(See the article by Linhares et al. on pages 312-4)

Recent estimates indicate that rotaviruses account for 39% of childhood gastroenteritis hospitalizations and ~611,000 rotavirus-related deaths, making rotaviruses the major cause of severe gastroenteritis in infants and young children worldwide [1].

In 1990, Ruuska and Vesikari [2] described a numerical scale to assess severity of gastroenteritis on the basis of duration and frequency of diarrhea and vomiting, fever, dehydration, and type of treatment required. The original Vesikari scale or scales based on similar criteria have been used to grade the severity of rotaviral diarrhea in epidemiological studies and vaccine trials [2, 3]. In this issue of Clinical Infectious Diseases, Linhares et al. [4] report an analysis of data from the placebo arm of a vaccine trial in Latin America that shows that circulating rotaviruses belonging to the genotype G9P[8] caused more-severe disease during the period of the trial than did rotaviruses belonging to other genotypes.

Group A rotaviruses, which are the major cause of human disease, are typed on the basis of the variability in the genes encoding the 2 outer capsid proteins—the outer capsid glycoprotein VP7 and the protease-cleaved spike protein VP4—into 15 G and 26 P genotypes, respectively [5]. Until 1990, rotavirus typing studies suggested that 4 common G and P combinations caused most documented rotaviral gastroenteritis [6]. Since then, intensive surveillance and molecular characterization studies have led to the recognition of additional strains that appear either to be important in specific settings or to be expanding their geographic distribution. Human G9 strains were first described in children with gastroenteritis in Philadelphia in 1983, but these strains disappeared during the next season [3]. At the end of the 1980s, rotaviruses later genotyped as G9P[11] strains were found in asymptotically infected neonates in India [7]. Subsequently, G9 strains, in association with the P[6] genotype, were found in Indian children with gastroenteritis. By 1995, they were being identified in other parts of the world as both G9P[6] and G9P[8] strains [8, 9]. They have now been identified on all inhabited continents, mainly as G9P[8] strains, and they accounted for 30% of strains detected in the study by Linhares et al. [4].

Despite their emergence and rapid global spread, data regarding an association between disease severity and G9 strains has been lacking since the initial report of G9P[6] strains causing disease in older children and more severe disease, documented when such strains were first detected in the United Kingdom [8]. The G9P[8] strains, which appeared shortly thereafter, may have emerged through reassortment in humans between G9P[6] strains and the more prevalent cocirculating G1, G3, and G4 strains with VP4 genes of P[8] serotype. Currently, G9P[8] strains seem to be the predominant G9 strains reported worldwide, but no increased severity was seen when this strain reappeared in Philadelphia, >10 years after it was originally described [3].

Most strain surveillance studies are hospital-based, with few studies describing the distribution of strains in the community. It can be argued that strains identified at presentation to the hospital are likely to be more severe and, therefore, more relevant to vaccine manufacturers and policy makers, but our understanding of transmission and disease would be incomplete without studies that investigate strain circulation in the community and also assess risk factors for severity, such as malnutrition, other comorbid conditions, and socioeconomic status. In the report by Linhares et al. [4], the study was prospective and community-based, resulting in a range of numerical scores from 2 to 20 on the Vesikari scale, indicating the broad spectrum of rotaviral disease in the community and demonstrating the high incidence of G9P[8] infections. The severity of these infections, as seen in these communities during the trial, raises some important points for consideration concerning strain virulence, previous exposure of the population, the role of maternal an-
tibodies in protection, clinical disease, and assessment of severity and the relevance of these factors to vaccine introduction.

Virulence of rotavirus strains has mainly been assessed in animal models and is associated with extensive spread of infection through the small intestine, preferential colonization of the proximal small intestine, and marked damage to enterocytes and villi [10]. There is, thus far, no evidence to suggest a difference in the virulence of G9 strains circulating in different parts of the world. Although G9P[11] strains are reported to cause mainly asymptomatic infections in neonates, maternal antibodies and the physiological immaturity of the gut may play a role in the lack of disease [11].

The introduction of a new strain into a naïve population should result in disease across all age groups, and this has been seen in rotavirus disease with outbreaks due to group B rotavirus [12]. With the introduction of G9 viruses into unexposed populations, extensive disease in adults has not been seen. This may be due to protection following prior exposure to other rotavirus strains or to a lack of susceptibility by as-yet-undefined mechanisms.

The lack of maternal antibodies to VP4 has been cited as a possible reason for neonatal infection with unusual rotoviral strains [11]. In the study by Linhares et al. [4], no children were infected from the time of recruitment until the age of at least 5 months, implying that maternal antibodies do play a role in protection from disease. In a community in which G9 viruses are newly introduced, maternal antibodies could protect only if antibodies against VP7 were responsible for heterotypic protection or if protection was mediated by antibodies against VP4. The latter hypothesis is supported by the fact that all strains in this study were of the P[8] serotype, to which the mothers are very likely to have had multiple exposures.

The effect of maternal protection can be expected to wane at 6 months of age or with cessation of breast feeding, and, indeed, most rotaviral disease is seen in children in the 6–24-month age group. Severe diarrhea and diarrheal mortality decrease in older children. However, in most hospital-based studies in which diarrheal severity is assessed, a single-point application of a severity scale is used at hospital presentation. In community-based longitudinal studies, assessments may be made at a routine surveillance visit, at presentation to a health care facility, or at the end of a diarrheal episode, and these could differ significantly from each other. In rotaviral infections, dehydration appears to be more common, although children appear to recover more quickly with rapid enteral hydration and shorter duration of hospitalization than with other agents of gastroenteritis [13].

In the report by Linhares et al. [4], data was captured both by routine surveillance after placebo administration and by survey of health care facilities, which would identify gastroenteritis episodes managed at home and those requiring hospitalization. Although the number of rotavirus infections is small, there is a clear difference between disease caused by G1 and G9 strains, both of which were associated with P[8] genotype, with no dehydrating gastroenteritis due to G1 viruses. Of interest, a recent report from Delhi, where the G9 strains have circulated for over a decade, showed that the previously less common G1 strains had increased in proportion during 2000–2001 and were causing significantly more-severe dehydration than G9 strains [14]. In Delhi, the G9 strains were associated mainly with P[6], and the G1 strains were associated mainly with P[8], making it more difficult to ascribe the difference in severity to the difference in G genotype alone. The data presented here offer important clues to understanding the basis of severity of rotaviral disease in a community, but they also emphasize the need for continued and intensive surveillance for rotaviral disease in countries considering the introduction of a rotaviral vaccine.

Acknowledgments

Potential conflicts of interest. G.K.: no conflicts.

References